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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

LE, EMILY M

ART UNIT

PAPER NUMBER

1648

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/733,686	Applicant(s) ILAN ET AL.	
	Examiner Emily Le	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03/11/2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37, 40-42, 45-49, 63 and 64 is/are pending in the application.
- 4a) Of the above claim(s) 46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37, 40-42, 45, 47-49 and 63-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/30/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. Claims 1-36, 38-39, 43-44 and 50-62 are cancelled. Claims 37, 40-42, 45-49 and 63-64 are pending. Claim 46 is withdrawn for being directed to a non-elected invention, which is HCV. Claims 37, 40-42, 45, 47-49 and 63-64 are under examination.

Information Disclosure Statement

2. Part of the information disclosure statement filed 10/30/2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. In instances where a copy of the literature was not provided, the information disclosed therein will not be considered. It has been placed in the application file, but the information referred to therein has not been considered. Additionally, the Office tried to search for document no. 10, WO 25/051986 in the foreign patents database, however, was unable to attain the document. It appears that the document number provided is incorrect.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of the claims under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicant's amendment.

5. Claims 37, 40-42, 45, 47-49 and 63-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the rejection, Applicant alleges that the Office has misconstrued the claimed invention and the enablement standard, and that the claimed invention is enabling. Applicant specifically argues that the test of enablement is not whether any experimentation is necessary but whether if experimentation is undue.

Applicant's arguments have been considered, however, they are not found persuasive. Applicant's reference to the test of enablement is correct. The test of enablement is whether one of skill in the art would be able to make and use the claimed invention without undue experimentation. In the instant case, using the Wands Factors, a prima facie case of undue experimentation has clearly been established by the Office in the enablement rejection. As noted in the enablement rejection, the elected invention for examination is a method of treating HCV in a mammal with the administration of a glycolipid. Yet, it is noted that Applicant has not taught nor demonstrated to the skilled artisan that the administration of any glycolipids treats HCV. All Applicant has demonstrated is an association between Gaucher's disease and hepatitis C virus infection. In the specification, Applicant notes that subjects diagnosed with Gaucher's disease and HCV infection have an immune profile that is different from those diagnosed with only Gaucher's disease, all of which is summarized in Figures 1-6 in the

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specification. Specifically, Applicant notes the following: i) HCV specific T cell proliferation and the percent of peripheral natural killer T lymphocytes are less in subjects diagnosed with both Gaucher's disease and HCV infection compared to those diagnosed with only Gaucher's diseases; and ii) the level of interferon gamma, interleukin-10 and interleukin 4 observed in subjects diagnosed with both Gaucher's disease and HCV are higher than those diagnosed with only Gaucher's diseases. In the instant, at the very best, the specification sets forth a nexus among various immune parameters, HCV and Gaucher's disease. The specification does not set forth any guidance or direction that would bridge the gap between the observations made by Applicant in the specification and the claimed invention, treating HCV with the glycolipid. There is no information provided in the specification detailing the type of immune parameter that should be modulated to treat HCV or any disease. There is no information provided in the specification regarding the specific immune parameter that a particular metabolite/glycolipid modulates and how the modulation results in the treatment of HCV. No such information or guidance is provided in the specification. While it is noted that Applicant submitted that pages 13-15 of the specification offers guidance to those skilled in the art with regard to both the specific compounds as well as specific disease to be treated with the claimed invention; however, it should be noted that theses are merely assertions or suggestions of use. The note disclosure is insufficient to enable the skilled artisan to practice the claimed invention without undue experimentation. In the instant case, the skilled artisan cannot rely on the disclosure set

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forth in the specification to reasonably practice the claimed invention without undue experimentation.

Regarding Applicant's allegation that the Office has misconstrued Applicant's claimed invention. Contrary to Applicant's assertion, such does not exist. In the instant case, the Office correctly construed the claimed invention. The claimed invention is directed to a method of treating HCV. From Applicant's disclosure, it is deduced that the nature of the claimed invention is directed at modulating the immune response in an individual with glycolipids to treat HCV. The desired immune response is a Th1 immune response, as detailed in the IFN-gamma data charted in the specification. Thus, contrary to Applicant's assertion, the Office has not misconstrued the claimed invention. Additionally, it should be noted that while the absence of any teachings relating to a mechanism of action does not necessarily render the claimed invention not enabling, such absence does not further enable the claimed invention when evaluated as a whole using the Wands Factors.

Additionally, as noted above, Applicant teaches that metabolites such as glycolipids modulate the immune profile; however, such does not commensurate with the claimed invention. The claimed invention is not directed at a method of modulating an immune response in an HCV infected person. Rather, the claimed invention is directed at a method of treating HCV in an HCV infected person. Thus, to be enabling for the claimed invention, Applicant must demonstrate that the skilled artisan would be able to practice the claimed invention without undue experimentation. In the instant

case, as discussed above and communicated in the rejection, Applicant has failed to provide an enabling disclosure.

Additional to above, Applicant argues that the specification contain working examples. To support Applicant's position, Applicant pointed out portions of the specification that provides written support for the language present in the claims.

Applicant's arguments have been considered, however, it is not found persuasive. The instant rejection is an enablement rejection, and not a written description rejection. As established in the rejection itself, Applicant failed to provide an enabling disclosure. The skilled artisan would not know how to practice the claimed invention without undue experimentations for Applicant has not demonstrated or provided any evidence that supports the treatment of HCV with a metabolite or glycolipid. All Applicant has provided is an association between patients that are HCV positive and have Gaucher's disease. This is merely an association study, which does not commensurate in scope with the claimed invention.

All that Applicant has provided in the specification is a suggestion of administering a reagent or metabolite, such as glycolipids, to treat HCV; yet the suggestion is not substantiated by any evidence demonstrating that glycolipids therapeutically treat HCV. What Applicant has is a method of modulating an immune component with the administration of a glycolipid. Such method does not commensurate with a method of treating HCV with the administration of glycolipids nor does it remotely relate to a therapeutic use of glycolipids to treat HCV. In the instant case, Applicant has not provided any guidance relating to the therapeutic use of

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glycolipids to treat HCV. All that Applicant has provided is the speculative use of glycolipids to modulate an immune component to treat HCV. Yet, Applicant fails to provide any guidance as to which immune component must be modulated, is the modulation an up regulation or down regulation, how much modulation is necessary, and if glycolipids are capable of providing the necessary modulation.

It is noted that specification discloses experiments that describes the impact of increased metabolite level, glycolipids, on the immune profile of HCV. However, it should be noted that the experiments fall short of demonstrating that glycolipids are therapeutically effective in treating HCV.

Regarding Applicant's assertion that the specification provides guidance as to the types of disease to which the present invention applies, it should be noted that this guidance is distinct from the guidance that would enable the skilled artisan to practice the claimed invention without an undue burden of experimentation. The guidance provided by Applicant is a suggestion of using glycolipids to treat various diseases, yet, the guidance does not teach or demonstrate that glycolipids are therapeutically effective in treating HCV infection. To enable the claimed invention, the guidance necessary is distinct from the guidance that is provided in the specification. As noted in the preceding paragraphs, all that the specification has provided is guidance on the speculative administration of glycolipids to treat various diseases, because it is found that glycolipids modulate an immune component. In the instant case, as it pertains to the elected invention, Applicant has not even described the immune component that must be modulated with the glycolipids, whether the modulation should be up or down, and

the threshold in which the modulation must take place in order to provide HCV treatment in a subject.

As noted in the rejection, the specification does not contain any working examples directed at the administration of glycolipids to treat HCV. The specification does not contain any working example relating to the effectiveness of glycolipids in treating HCV. In the absence of the any working examples, the skilled artisan would not readily be able to practice the claimed invention without experimentation. Compounded further by the absence of any guidance or direction directing or evidencing the therapeutic use of glycolipids to treat HCV, the experimentation required of the skilled artisan would be sufficient to be undue experimentation. Affirmation of this burden of undue experimentation on the skilled artisan practicing the claimed invention is further provided by the challenges recognized in the HCV art, such as an absence of good animal models, besides humans and chimpanzees, the ability of HCV to evade effective immune recognition, the high rate of viral persistence, absence of an effective cell culture system for HCV, and the lack of understanding on the role of innate and antigen-nonspecific immune response to HCV, all of which is discussed below. In view of a nonenabling disclosure, the skilled artisan in the HCV art would not be able to seek any guidance, direction or relief from the HCV art in practicing the claimed invention.

Thus, in view of the discussion provided above, it is found that Applicant's arguments are not persuasive. Therefore, the claims remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

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As previously presented, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Nature of the invention:

The claimed invention is directed at the treatment of diseases, wherein the elected disease is hepatitis C virus, HCV, with the administration of a glycolipid. As noted by Applicant, the claimed invention relates to the application of glycolipid to regulate and manipulate immune responses, Th1 and Th2 responses, in mammalian subjects to treat mammalian subjects of an infection, particularly wherein the elected infection is hepatitis C virus. [First paragraph, Field of the invention, page 1 of specification.]

Breadth of the claims:

The claims encompass all diseases, wherein the elected disease is hepatitis C virus; all mammalian subjects, and glycolipids.

Presence or absence of working examples and Amount of direction or guidance presented:

The specification does not contain any working examples demonstrating the effective use of glycolipids to treat HCV infection. All that is present in the specification is an association study, which demonstrates that HCV infected subjects have a different immune profile if they are also diagnosed with Gaucher's disease, compared to those that are not diagnosed with Gaucher's disease, where there is a buildup of glucosylcerebroside (glycolipid) due to the decreased capacity for breakdown of this product. Through this association study, Applicant suggests the administration of glycolipids to treat HCV infection by modulating a change in at least one immune component. [Paragraph bridging pages 12-13, in particular.] However, Applicant has not set forth any guidance or direction relating to the immune component that must be changed or modulated in order to render treatment to HCV infected subjects. What is the immune component that must be modulated or changed? Is it a Th1 or Th2 immune response that must be induced? What kind of Th1 or Th2 induced cytokines must be produced in order to effectively treat HCV? Is this modulation or change directed at increasing or decreasing the activity of this particular immune component? And are glycolipids capable of rendering this change or modulation? In the instant case, beyond the speculative use of glycolipids to treat HCV, Applicant has not provided any

additional information or evidence regarding the effective use of glycolipids to treat HCV infection.

State of the prior art:

The hepatitis C virus (HCV) art clearly notes that the role of innate and antigen-nonspecific immune response to HCV has not yet been sufficiently characterized.¹ In the absence of a sufficient characterization of the role of innate and antigen-nonspecific immune responses to HCV, the skilled artisan would not readily be able to practice the claimed invention without an undue burden of experimentation. In the absence of such characterization, the burden is on the skilled artisan to mine the field to determine significance of the innate and antigen-nonspecific in HCV treatment. The art additionally acknowledges several factors that challenge the development of an effective treatment for HCV.^{2, 3, 4}

The first factor is the lack of an effective cell culture system for HCV. In the absence of an effective cell culture system for HCV, the skilled artisan would be at an immediate disadvantage when it comes researching the effects of innate or antigen-nonspecific immune responses in HCV treatment. The second challenge is the absence of good animal models for HCV, outside of humans and chimpanzees. In the instant case, the noted disadvantage that the skilled artisan would face in practicing the

¹ Knipe DM, Howley PM, eds. Fields virology. 4th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins, 2001, 1004-1016 and 1127-1161.

² Hahn. Subversion of immune responses by hepatitis C virus: immunomodulatory strategies beyond evasion? Current opinion in Immunology, 2003, Vol. 15, 443-449.

³ Knipe DM, Howley PM, eds. Fields virology. 4th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins, 2001, 1004-1016 and 1127-1161.

⁴ De Francesco et al. Challenges and successes in developing new therapies of hepatitis C. Nature, 2005, Vol. 436, 953-960.

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claimed invention is further compounded by the noted absence of good animal models for HCV. Combined, in the absence of an effective in vitro and in vivo model for conduct HCV research, a prima facie case of undue experimentation and unpredictability is established. The other challenge is the ability of HCV to evade effective immune recognition, including recognition by cytotoxic T lymphocytes (CTL), and shows an extremely high rate of viral persistence. In the instant case, it should be noted that Applicant has not taught the skilled artisan how to deal or address each of the challenges addressed herein. This last point further establishes that the type of experimentation that the skilled artisan would have to perform in practicing the claimed invention is beyond routine experimentation, such as establishing route of administration and treatment dosage amounts. The imposition of experimentations that is beyond routine experimentation would unduly burden the skilled artisan practicing the claimed invention.

Quantity of experimentation necessary:

The skilled artisan cannot rely on the disclosure set forth in the specification to reasonably practice the invention without the burden of undue experimentation. In order for the skilled artisan to successfully practice the claimed invention, the skilled artisan would have to blindly and unduly experiment with glycolipids, each immune component, and determine the relationship among the glycolipids, each immune components and HCV infection.

In all, the skilled artisan practicing the claimed invention would have to bridge the gap between the glycolipids and HCV infection, the gap that should have been

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substantially filled by Applicant, at the time the invention was filed. In the instant case, the attainment of such knowledge would undeniably be an undoubtedly laborious task that includes both blind and undue experimentations. And the imposition of both blind and undue experimentations would unarguably be an undue burden for the skilled artisan.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Conclusion

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Le/
Primary Examiner, Art Unit 1648

/E. L./